Contents

Proceedings of the International Congress of Toxicology—VII

Preface xv

Deichmann Lecture

1995 Deichmann Lecture—p53 tumor suppressor gene: at the crossroads of molecular carcinogenesis, molecular epidemiology and cancer risk assessment
C.C. Harris (USA) 1

Symposium: Cell Proliferation: Biological Effects and Carcinogenic Risk Assessment

Cell proliferation as a determining factor for the carcinogenicity of chemicals: studies with mutagenic carcinogens and mutagenic noncarcinogens
M.L. Cunningham, H.B. Matthews (USA) 9

Role of cell proliferation in regenerative and neoplastic disease
S.M. Cohen (USA) 15

The role of regenerative cell proliferation in chloroform-induced cancer
B.E. Butterworth, M.V. Templin, S.J. Borghoff, R.B. Conolly, G.L. Kedderis, D.C. Wolf (USA) 23

Role of cell proliferation at early stages of hepatocarcinogenesis
M. Schwarz, A. Buchmann, K.-W. Bock (Germany) 27

Symposium: Asthma and the Environment

Asthma and the environment: do environmental factors affect the incidence and prognosis of asthma?
J.M. Samet (USA) 33

Occupational asthma
S.M. Brooks (USA) 39

Environmentally induced asthma
M.J. Utell, R.J. Looney (USA) 47

Symposium: Recent Advances in Pesticide Toxicology

Recent epidemics of poisoning by pesticides
A. Ferrer, R. Cabral (Spain, Japan) 55

Pesticide exposure assessment
R.I. Krieger (USA) 65

Pesticide-metabolizing enzymes
E. Hodgson, R.L. Rose, D.-Y. Ryu, G. Falls, B.L. Blake, P.E. Levi (USA) 73

Molecular biology of insecticide resistance
R. Feyereisen (USA) 83

Workshop: The Integration of Investigative Toxicology in the Drug Discovery and Development Process

Receptors as tools for understanding the toxicity of retinoids
A.A. Levin (USA) 91

Pancreatic and nephrotoxicity of immunomodulator compounds
T.G. Hammond, C.N. Kind (UK) 99

Cultured hepatocytes as investigational models for hepatic toxicity: practical applications in drug discovery and development
R.G. Ulrich, J.A. Bacon, C.T. Cramer, G.W. Peng, D.K. Petrella, R.P. Stryd, E.L. Sun (USA) 107

Symposium: In Vivo Transgenic Models
Xenobiotic receptor knockout mice
F.J. Gonzalez, P. Fernandez-Salguero, S.S.T. Lee, T. Pineau, J.M. Ward (USA) 117
Transgenic approaches to understanding the mechanisms of chemical carcinogenesis in mouse skin
K. Brown, P.A. Burns, A. Balmain (UK) 123
Transgenic models for detection of mutations in tumors and normal tissues of rodents
J.C. Mirsalis (USA) 131

Symposium: Apoptosis in Toxicology
DNA degradation and proteolysis in thymocyte apoptosis
H.O. Fearnhead, M. MacFarlane, D. Dinsdale, G.M. Cohen (UK) 135
Role of active cell death (apoptosis) in multi-stage carcinogenesis
R. Schulte-Hermann, W. Bursch, B. Grasl-Kraupp, L. Török, A. Ellinger, L. Müllauer (Austria) 143
Signalling mechanisms and oxidative stress in apoptosis
A.F.G. Slater, C. Stefan, I. Nobel, D.J. van den Dobbelsteen, S. Orrenius (Sweden) 149
Bcl-2 family proteins: regulators of chemoresistance in cancer
J.C. Reed (USA) 155

Symposium: Chemopreventive Agents and Anticancer Drugs: Therapy and Toxicity
Modulators of signal transduction as cancer chemotherapeutic agents – novel mechanisms and toxicities
A. Gescher (UK) 159
Anticancer drug toxicity via cytokine production: the hydroxyurea paradigm
P. Navarra, P. Puccetti, C. Riccardi, P. Preziosi (Italy) 167
Chemoprotection against cancer by Phase 2 enzyme induction
P. Talalay, J.W. Fahey, W.D. Holtzclaw, T. Prestera, Y. Zhang (USA) 173
Chemoprevention of breast cancer by tamoxifen: risks and opportunities
L.L. Smith, I.N.H. White (UK) 181

Workshop: Behavioral (Cognitive) Toxicology
A few considerations in the design and analysis of experiments in neurotoxicology
J.P.J. Maurissen (USA) 187
The use of neurobehavioural test batteries for research, diagnosis and screening: methodological aspects
A. Spurgeon (UK) 191
Neurobehavioral assessment in toxic injury evaluations
P.R. Lees-Haley (USA) 197
Neurobehavioural test batteries: current status, critical evaluation and new directions
A.M. Williamson (Australia) 203

Workshop: Risk Communication
Media and risk commumication
I. Atterstam (Sweden) 211

Symposium: Toxicology of Endogenous Nitric Oxide
Inhibition of biotransformation by nitric oxide (NO) overproduction and toxic consequences
J. Stadler, W.A. Schmalix, J. Doehmer (Germany) 215
Nitric oxide (NO) protects against cellular damage by reactive oxygen species
D.A. Wink, J.A. Cook, R. Pacelli, J. Liebmann, M.C. Krishna, J.B. Mitchell (USA) 221
Tolerance against tumor necrosis factor α (TNF)-induced hepatotoxicity in mice: the role of nitric oxide
I. Bohlinger, M. Leist, J. Barsig, S. Uhlig, G. Tiegs, A. Wendel (Germany) 227
The role of nitric oxide in cell injury
B. Brüne, U.K. Meßmer, K. Sandau (Germany) 233

Symposium: Neurotoxicology
Sodium channels and $GABA_A$ receptor-channel complex as targets of environmental toxicants
T. Narahashi, D.B. Carter, J. Frey, K. Ginsburg, B.J. Hamilton, K. Nagata, M.L. Roy, J.-H. Song, H. Tatebayashi (USA) 239
Towards the development of ryanoid insecticides with low mammalian toxicity
P.N.R. Usherwood, H. Vais (UK) 247

Calcium channels as target sites of heavy metals
D. Büsselberg (Germany) 255
Molecular mechanism of the lead-induced inhibition of rod cGMP phosphodiesterase
D.A. Fox, D. Srivastava (USA) 263
Influence of toxicants on neural cell adhesion molecule-mediated neuroplasticity in the developing and adult animal: persistent effects of chronic perinatal low-level lead exposure
K.J. Murphy, G.B. Fox, J. Kelly, C.M. Regan (Ireland) 271

Symposium: Ozone and the Environment
Uptake and fate of ozone in the respiratory tract
F.J. Miller (USA) 277
A new mechanism for the toxicity of ozone
W.A. Pryor, G.L. Squadrito, M. Friedman (USA) 287
Genetic susceptibility to ozone exposure
S.R. Kleeberger (USA) 295
Long-term toxicity studies of ozone in F344/N rats and B6C3F1 mice
G.A. Boorman, R.C. Sills, S. Grumbein, R. Hailey, R.A. Miller, R.A. Herbert (USA) 301
Ozone-induced human respiratory dysfunction and disease
P.A. Bromberg, H.S. Koren (USA) 307
Dose-effect models for ozone exposure: tool for quantitative risk estimation
L. van Bree, M. Marra, H.J. van Scheindelen, P.H. Fischer, S. de Loos, E. Buringh, P.J.A. Rombout (The Netherlands) 317

Workshop: Methods of Analysis for Detecting Genomic Alterations
Analysis of mutation at the *hprt* locus in human T lymphocytes
B. Lambert, T. Bastlova, A.-M. Österholm, S.-M. Hou (Sweden) 323
A microassay for measuring cytosine DNA methyltransferase activity during tumor progression
S.A. Belinsky, K.J. Nikula, S.B. Baylin, J.-P. Issa (USA) 335

Workshop: Toxicokinetics and Physiologically-Based Pharmacokinetics (PB-PK)
Physiologically based pharmacokinetic (PB-PK) models in the study of the disposition and biological effects of xenobiotics and drugs
M.E. Andersen (USA) 341
Applications and prospects for physiologically based pharmacokinetic (PB-PK) models involving pharmaceutical agents
H. Suzuki, T. Iwatsubo, Y. Sugiyama (Japan) 349
Toxicokinetic models for volatile industrial chemicals and reactive metabolites
J.G. Filser, G.A. Csanády, P.E. Kreuzer, W. Kessler (Germany) 357
PBK modeling for metals. Examples with lead, uranium, and chromium
E.J. O'Flaherty (USA) 367

Symposium: Biomarkers of Exposure
Case studies of the use of biomarkers to assess exposures
L.L. Needham, D.L. Ashley, D.G. Patterson Jr (USA) 373
Strategies for use of biological markers of exposure
R.F. Henderson (USA) 379
Markers for immunotoxic effects in rodents and man
J.G. Vos, H.V. Loveren (The Netherlands) 385

Symposium: Oxidative Stress in Cell Injury
Glutathione peroxidase and oxidative stress
J.H. Doroshow (USA) 395
Amplification of glutamate-induced oxidative stress
K.M. Savolainen, J. Loikkanen, J. Naarala (Finland) 399
Function and activation of the transcription factor NF-κB in the response to toxins and pathogens
M.L. Schmitz (Germany) 407
Effects of oxidative stress induced by redox-enzyme modulation on rat hepatocarcinogenesis
A. Denda, T. Endoh, D. Nakae, Y. Konishi (Japan) 413

Workshop: Antisense Therapy: Toxicological Impact
Antisense phosphorothioate oligodeoxynucleotides: introductory concepts and possible molecular mechanisms of toxicity
G. Zon (USA) 419
Pharmacology and toxicology of phosphorothioate oligonucleotides in the mouse, rat, monkey and man
P.L. Iversen, B.L. Copple, H.K. Tewary (USA) 425
Novel enzymatic and immunological responses to oligonucleotides
S. Agrawal, P.K. Rustagi, D.R. Shaw (USA) 431
Antisense phosphorothioates as antivirals against human immunodeficiency virus (HIV) and hepatitis B virus (HBV)
M. Matsukura, K. Koike, G. Zon (Japan, USA) 435

Workshop: Molecular Mechanism and Clinical Significance Of Esterase-Oriented Actions: Reassessment of Their Classification
Molecular aspects of carboxylesterase isoforms in comparison with other esterases
T. Satoh, M. Hosokawa (Japan) 439
Catalytic properties and distribution profiles of paraoxonase and cholinesterase phenotypes in human sera
E. Reiner, V. Simeon-Rudolf, M. Skrinjaric-Spoljar (Croatia) 447
Structural bases for the specificity of cholinesterase catalysis and inhibition
P. Taylor, Z. Radic, N.A. Hosea, S. Camp, P. Marchot, H.A. Berman (USA) 453
Neuropathy target esterase (NTE) and organophosphorus-induced delayed polyneuropathy (OPIDP): recent advances
M.K. Johnson, P. Glynn (UK) 459

Plenary Lecture
Receptor-mediated toxicity
J.-Å. Gustafsson (Sweden) 465

Symposium: Role of Proinflammatory Cytokines in Mediating Chemical and Drug-related Toxicity
Role of keratinocyte-derived cytokines in chemical toxicity
M.I. Luster, J.L. Wilmer, D.R. Germolec, J. Spalding, T. Yoshida, K. Gaido, P.P. Simeonova, F.G. Burleson, A. Bruccoleri (USA, Japan) 471
Role of proinflammatory cytokines in a toxin response: application of cytokine knockout mice in toxicological research
B. Ryffel (Switzerland) 477
TNFα and increased chemokine expression in rat lung after particle exposure
K.E. Driscoll, D.G. Hassenbein, J.M. Carter, S.L. Kunkel, T.R. Quinlan, B.T. Mossman (USA) 483
Cytokine regulation of chemical sensitization
I. Kimber, M.R. Holliday, R.J. Dearman (UK) 491

Symposium: Chemical Mixtures: Toxicological Impacts and Interactive Effects
The use of physiologically-based pharmacokinetic/pharmacodynamic dosimetry models for chemical mixtures
R.S.H. Yang, H.A. El-Masri, R.S. Thomas, A.A. Constan (USA) 497
Toxicity studies in rats of simple mixtures of chemicals with the same or different target organs
V.J. Feron, J.P. Groten, J.A. van Zorge, F.R. Cassee, D. Jonker, P.J. van Bladeren (The Netherlands) 505
Lack of carcinogenicity of pesticide mixtures administered in the diet at acceptable daily intake (ADI) dose levels in rats
N. Ito, A. Hagiwara, S. Tamano, R. Hasegawa, K. Imaida, M. Hirose, T. Shirai (Japan) 513
Health risk assessment of chemical mixtures from a research perspective
J.A. Bond, M.A. Medinsky (USA) 521
Risk assessment of chemical mixtures from a public health perspective
M.M. Mumtaz (USA) 527

Symposium: Developmental and Reproductive Hazard Assessment: Recent Advances
Regulatory and political perspectives in reproductive and developmental hazard assessment
F.M. Sullivan (UK) 533
Physiologically based pharmacokinetic models applicable to organogenesis: extrapolation between species and potential use in prenatal toxicity risk assessments
F. Welsch, G.M. Blumenthal, R.B. Conolly (USA) 539
The application of benchmark dose methodology to data from prenatal developmental toxicity studies
C.A. Kimmel, R.J. Kavlock, B.C. Allen, E.M. Faustman (USA) 549

Application of benchmark dose risk assessment methodology to developmental toxicity: an industrial view
P.M.D. Foster, T.R. Auton (UK) 555

Workshop: Protein-DNA Interactions: Analysis By ESR, NMR and Mass Spectrometry
In vivo ESR measurements of free radical reactions in living mice
H. Utsumi, K. Ichikawa, K. Takeshita (Japan) 561
Mass spectrometric approaches to molecular characterization of protein-nucleic acid interactions
M. Przybylski, J. Kast, M.O. Glocker, E. Dürr, H.R. Bosshard, S. Nock, M. Sprinzl (Germany, Switzerland) 567
Multidimensional NMR spectroscopy of DNA-binding proteins: structure and function of a transcription factor
V.L. Hsu, X. Jia, D.R. Kearns (USA) 577
Structure and dynamics of the *lac* repressor-operator complex as determined by NMR
R. Kaptein, M. Slijper, R. Boelens (The Netherlands) 591

Symposium: Genetic Susceptibility to Toxicity
Genetic and environmental factors in the etiology of human brain tumors
P. Kleihues, A. Aguzzi, H. Ohgaki (France, Switzerland) 601
The use of transgenic mice for studying mutagenicity induced by 1,3-butadiene
L. Recio, T.L. Goldsworthy (USA) 607
Genetics of liver tumor susceptibility in mice
T.A. Dragani, G. Manenti, M. Gariboldi, L. De Gregorio, M.A. Pierotti (Italy) 613
Hereditary renal cell carcinoma in the Eker rat: a unique animal model for the study of cancer susceptibility
J.I. Everitt, T.L. Goldsworthy, D.C. Wolf, C.L. Walker (USA) 621
Genetic susceptibility and carcinogen-DNA adduct formation in human urinary bladder carcinogenesis
F.F. Kadlubar, A.F. Badawi (USA) 627

Symposium: Xenobiotic Metabolism in Brain
Xenobiotic metabolism in brain
V. Ravindranath, S. Bhamre, S.V. Bhagwat, H.K. Anandatheerthavarada, S.K. Shankar, P.S. Tirumalai (India) 633
Expression of multiple forms of brain cytochrome P450
H.W. Strobel, H. Kawashima, J. Geng, D. Sequeira, A. Bergh, A.V. Hodgson, H. Wang, S. Shen (USA) 639
Blood-brain interfaces: relevance to cerebral drug metabolism
J.F. Ghersi-Egea, B. Leininger-Muller, R. Cecchelli, J.D. Fenstermacher (France, USA) 645
Localization and characterization of cytochrome P450 in the brain. In vivo and in vitro investigations on phenytoin- and phenobarbital-inducible isoforms
B. Volk, R.P. Meyer, F. von Lintig, B. Ibach, R. Knoth (Germany) 655

Workshop: Non-Genotoxic Chemical Carcinogenesis
Hypomethylation of DNA: a nongenotoxic mechanism involved in tumor promotion
J.L. Counts, J.I. Goodman (USA) 663
Peroxisome proliferation: current mechanisms relating to non-genotoxic carcinogenesis
B.G. Lake (UK) 673
Oxidative stress in nongenotoxic carcinogenesis
J.E. Klaunig, Y. Xu, S. Bachowski, C.A. Ketcham, J.S. Isenberg, K.L. Kolaja, T.K. Baker, E.F. Walborg Jr., D.E. Stevenson (USA) 683
Clofibrate-induced neoplastic development in the rat liver is associated with decreased connexin 32 expression but not with a co-ordinated shift in expression of marker enzymes
H. Tsuda, M. Asamoto, H. Baba-Toriyama, Y. Iwahori, T. Hori, D.J. Kim, T. Tsuchiya, M. Mutai, H. Yamasaki (Japan, France) 693
Role of blocked gap junctional intercellular communication in non-genotoxic carcinogenesis
M. Mesnil, V. Krutovskikh, Y. Omori, H. Yamasaki (France) 701

Workshop: Health Risks of Oxygenated Motor Vehicle Fuels
Recent developments in methanol toxicity
M.A. Medinsky, D.C. Dorman (USA) 707
Toxicokinetics and acute effects of MTBE and ETBE in male volunteers
G. Johanson, A. Nihlén, A. Löf (Sweden) 713
Health effects of inhaled tertiary amyl methyl ether and ethyl tertiary butyl ether
R.D. White, W.C. Daughtrey, M.S. Wells (USA) 719

Plenary Lecture
Can chemicals be loved? – A problem for 2000
C. Berry (UK) 725

Symposium: Estrogenic and Antiestrogenic Activities of Chemicals in the Environment
Chlorinated hydrocarbons: estrogens and antiestrogens
S. Safe, V. Krishnan (USA) 731
Feminized responses in fish to environmental estrogens
J.P. Sumpter (UK) 737
Developmental effects of dioxins and related endocrine disrupting chemicals
L.S. Birnbaum (USA) 743

Symposium: Biomarkers and Molecular Interactions: Implications for Human Risks
Dose-response relationships for carcinogens
J.A. Swenberg, D.K. La, N.A. Scheller, K.-y. Wu (USA) 751
Monitoring of human exposure to carcinogens through DNA and protein adduct determination
P.B. Farmer (UK) 757
Molecular epidemiology and human risk monitoring
J.D. Groopman, T.W. Kensler, J.M. Links (USA) 763
The implications for risk assessment of measuring the relative contribution to exposure from occupation, environment and lifestyle: hemoglobin adducts from amino- and nitro-arenes
H.-G. Neumann, C. van Dorp, I. Zwirner-Baier (Germany) 771

Workshop: Antidotes: Mechanisms of Action
Antidotes: benefits and risks
A.T. Proudfoot (UK) 779
Modifying toxicokinetics with antidotes
F.J. Baud, S.W. Borron, C. Bismuth (France) 785
Modification of cyanide toxicodynamics: mechanistic based antidote development
G.E. Isom, J.L. Borowitz (USA) 795
Drug-specific antibodies as antidotes for tricyclic antidepressant overdose
P.R. Pentel, D.E. Keyler (USA) 801

Workshop: Genetically Engineered Models for Study of Biotransformations
Genetically engineered bacterial cells and applications
M.R. Waterman, C.M. Jenkins, I. Pikuleva (USA) 807
Genetically engineered yeast cells and their applications
D. Pompon, A. Perret, A. Bellamine, R. Laine, J.-C. Gautier, P. Urban (France) 815
Genetically engineered mammalian cells and applications
J. Doehmer, A. Schneider, M. Faßbender, V. Soballa, W.A. Schmalix, H. Greim (Germany) 823
Salmonella strains and mammalian cells genetically engineered for expression of sulfotransferases
H. Glatt, I. Bartsch, A. Czich, A. Seidel, C.N. Falany (Germany, USA) 829

Debate: Exposure to Synthetic Chemicals is More Hazardous Than Exposure to Natural Chemicals
The hazards of synthetic (anthropogenic) chemicals
E.K. Silbergeld (USA) 835

Symposium: The Mycotoxins of Human Concern
Mycotoxins, general view, chemistry and structure
P.S. Steyn (Republic of South Africa) 843
Mycotoxins: risk assessment and legislation
T. Kuiper-Goodman (Canada) 853
Genetic implications in the metabolism and toxicity of mycotoxins
G.E. Neal (UK) 861
Prevention of nephrotoxicity of ochratoxin A, a food contaminant
E.E. Creppy, I. Baudrimont, A.-M. Betbeder (France) 869

Symposium: Genetically Engineered Mammalian Cell Systems

Expression of CYP3A7, a human fetus-specific cytochrome P450, in cultured cells and in the hepatocytes of p53-knockout mice
T. Kamataki, H. Hashimoto, M. Shimoji, S. Itoh, K. Nakayama, K. Hattori, T. Yokoi, M. Katsuki, S. Aizawa (Japan) 879

Genetically modified Chinese hamster ovary (CHO) cells for studying the genotoxicity of heterocyclic amines from cooked foods
L.H. Thompson, R.W. Wu, J.S. Felton (USA) 883

Symposium: Role of Toxicology in Tomorrow's Risk Assessment Practices

Injury and repair as opposing forces in risk assessment
H.M. Mehendale (USA) 891

Biologically based dose response model for hepatic toxicity: a mechanistically based replacement for traditional estimates of noncancer risk
R.B. Conolly, B.E. Butterworth (USA) 901

Mechanisms in tumor promotion: guidance for risk assessment and cancer chemoprevention
F. Marks, G. Fürstenberger, T. Heinzelmann, K. Müller-Decker (Germany) 907

Understanding mechanisms of inhaled toxicants: implications for replacing default factors with chemical-specific data
M.S. Bogdanffy, A.M. Jarabek (USA) 919

Pyrethroids, nerve poisons: how their risks to human health should be assessed
J. Miyamoto, H. Kaneko, R. Tsuji, Y. Okuno (Japan) 933

Workshop: Role of Iron in Chemical-induced Toxicities

Ferritin as a source of iron and protection from iron-induced toxicities
S.D. Aust (USA) 941

Synergy of iron in the toxicity and carcinogenicity of polychlorinated biphenyls (PCBs) and related chemicals
A.G. Smith, P. Carthew, B. Clothier, D. Constantin, J.E. Francis, S. Madra (UK) 945

Role of iron in the reactivity of mineral fibers
B. Fubini, L. Mollo (Italy) 951

Potential protection from toxicity by oral iron chelators
R.C. Hider (UK) 961

Toxicity of iron and hydrogen peroxide: the Fenton reaction
C.C. Winterbourn (New Zealand) 969

Late submission

Chemical structure – teratogenicity relationships, toxicokinetics and metabolism in risk assessment of retinoids
H. Nau (Germany) 975

Author index Vols. 82/83 981

Subject index Vols. 82/83 989